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TECHNICAL REPORT

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Combined Injury Modeling: Radiation and Burn Workshop Report

Approved for public release; distribution is unlimited

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CONVERSION TABLE

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MULTIPLY →	BY →	TO GET
TO GET ←	BY ←	DIVIDE

angstrom	1.000 000 x E -10	meters (m)
atmosphere (normal)	1.013 25 x E +2	kilo pascal (kPa)
bar	1.000 000 x E +2	kilo pascal (kPa)
barn	1.000 000 x E -28	meter^2 (m^2)
British thermal unit (thermochemical)	1.054 350 x E +3	joule (J)
calorie (thermochemical)	4.184 000	joule (J)
cal (thermochemical/cm^2)	4.184 000 x E -2	mega joule/m^2 (MJ/m^2)
curie	3.700 000 x E +1	giga becquerel (GBq)*
degree (angle)	1.745 329 x E -2	radian (rad)
degree Fahrenheit	$t_k = (t^of + 459.67)/1.8$	degree kelvin (K)
electron volt	1.602 19 x E -19	joule (J)
erg	1.000 000 x E -7	joule (J)
erg/second	1.000 000 x E -7	watt (W)
foot	3.048 000 x E -1	meter (m)
foot-pound-force	1.355 818	joule (J)
gallon (U.S. liquid)	3.785 412 x E -3	meter^3 (m^3)
inch	2.540 000 x E -2	meter (m)
jerk	1.000 000 x E +9	joule (J)
joule/kilogram (J/kg) radiation absorbed dose	1.000 000	gray (Gy)**
kilotons	4.183	terajoules
kip (1000 lbf)	4.448 222 x E +3	newton (N)
kip/inch^2 (ksi)	6.894 757 x E +3	kilo pascal (kPa)
ktap	1.000 000 x E +2	newton-second/m^2 (N-s/m^2)
micron	1.000 000 x E -6	meter (m)
mil	2.540 000 x E -5	meter (m)
mile (international)	1.609 344 x E +3	meter (m)
ounce	2.834 952 x E -2	kilogram (kg)
pound-force (lbs avoirdupois)	4.448 222	newton (N)
pound-force inch	1.129 848 x E -1	newton-meter (N-m)
pound-force/inch	1.751 268 x E +2	newton/meter (N/m)
pound-force/foot^2	4.788 026 x E -2	kilo pascal (kPa)
pound-force/inch^2 (psi)	6.894 757	kilo pascal (kPa)
pound-mass (lbm avoirdupois)	4.535 924 x E -1	kilogram (kg)
pound-mass-foot^2 (moment of inertia)	4.214 011 x E -2	kilogram-meter^2 (kg-m^2)
pound-mass/foot^3	1.601 846 x E +1	kilogram-meter^3 (kg/m^3)
rad (radiation dose absorbed)	1.000 000 x E -2	gray (Gy)**
roentgen	2.579 760 x E -4	coulomb/kilogram (C/kg)
shake	1.000 000 x E -8	second (s)
slug	1.459 390 x E +1	kilogram (kg)
torr (mm Hg, 0^0 C)	1.333 22 x E -1	kilo pascal (kPa)

*The becquerel (Bq) is the SI unit of radioactivity; 1 Bq = 1 event/s.
**The gray (Gy) is the SI unit of absorbed dose.

ABSTRACT

This report provides an overview of the DTRA-sponsored workshop on combined injury (CI) modeling held on June 22, 2010. During this workshop, a panel of subject matter experts assembled by Applied Research Associates discussed acute radiation injury combined with thermal burn injury. Participants provided input on the primary organ systems affected by CI, underlying mechanisms associated with CI, modeling approaches, recommended tools, and possible simplifying assumptions for modeling radiation injury combined with burn. Workshop participants also noted gaps in knowledge and potential paths forward. Workshop outcomes include a diagram that illustrates key pathophysiological processes associated with radiation injury and burn; these processes are primary candidates for modeling efforts.

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1. INTRODUCTION

As part of its mission to safeguard against weapons of mass destruction (WMD), the Defense Threat Reduction Agency (DTRA) supports the development of capabilities to reduce, eliminate and counter WMD threats and mitigate their effects. Applied Research Associates (ARA) has been tasked by DTRA to support this effort by developing state-of-the-art mathematical models that predict medical and performance consequences from radiation and combined injuries, thereby enhancing our understanding of the potential impact of a nuclear detonation. ARA aims to improve current casualty estimation capabilities through an interdisciplinary approach integrating experimental data with mechanistic mathematical modeling. An effort to build a mechanistic model of acute radiation sickness based on physiology was undertaken in the 1990's. The result was the Radiation-Induced Performance Decrement (RIPD) model, which was integrated into a software tool used for planning and scenario predictions for nuclear detonations (Matheson 1998).

However, in nuclear detonation scenarios, a number of diverse injuries could be anticipated including blunt trauma, open wounds, and burn, all of which could be complicated by microbial infection. From historical data from Hiroshima, 65-70% of injured persons are expected to have combined injuries, the majority of which will have radiation combined with burn (Geiger 1964, Goans 2009). Experimental data has shown that radiation combined with other injuries shortens the onset of symptoms, exacerbates symptoms, causes synergistic increases in mortality, and impairs wound healing (Messerschmidt 1965; Baum 1991). To improve our understanding of human response to combined injury, an initiative is underway to model radiation combined injury. The existing combined injury model, Combined Human Response Nuclear Effects Model (CHRNEM), is based strictly on empirical descriptions of signs and symptoms (Levin 1993) and lacks descriptions of the physiological mechanisms behind injury. Therefore, a long-term goal of this modeling initiative is to move from existing empirical models to mechanistic models that describe the biological processes of combined injury – beginning with radiation combined with burn. Such capabilities will not only serve to improve casualty estimations and performance decrements in combined injuries, but the knowledge that evolves with this process will also provide insight into potential avenues for improved countermeasures.

The effort to establish physiologically-based, mechanistic models for combined injury requires a wide range of expertise. Therefore, a panel of subject matter experts (SMEs) was assembled for a workshop aimed at providing collective insight on radiation combined with burn injury by discussing different aspects of radiation health effects, burn injury, and mathematical modeling approaches. The panel, their affiliations, and areas of expertise are listed in Table 1.

The DTRA sponsored workshop was held on June 22, 2010 at the ARA offices in Ballston. In addition to the SME panel and the ARA scientific team, representatives from several federal agencies with an interest in combined injury or casualty estimations attended the workshop. Kyle Millage, the principal investigator of the Human Survivability project at ARA, introduced the topic of the workshop and the role ARA has in the initiative. Dr. Glen Reeves represented

Table 1. Panel of Subject Matter Experts

Name	Affiliation	Expertise
Mary Helen Barcellos-Hoff, Ph.D.	New York University	Systems radiobiology
Bruce Cairns, M.D.	University of North Carolina	Burn injury
LTC John Cuellar	Uniformed Services University of the Health Sciences	Health physics
Francis Hérodin, Ph.D.	Centre de Recherches du Service de Santé des Armées	Acute radiation syndrome, radiation hematology
Juliann Kiang, Ph.D.	Armed Forces Radiobiology Research Institute	Radiobiology
COL Viktor Meineke, M.D.	Bundeswehr Institute of Radiobiology	Acute radiation syndrome, cutaneous injury
Alla Shapiro, M.D., Ph.D.	Food and Drug Administration	Clinical radiation effects, beta burns
William Smith, Ph.D.	U.S. Army Medical Research Institute of Chemical Defense	Chemical burns and cutaneous injury
Yoram Vodovotz, Ph.D.	University of Pittsburgh	Mathematical modeling in biology
Eberhard Voit, Ph.D.	Georgia Institute of Technology	Computational biology
Jacqueline Williams, Ph.D.	University of Rochester	Radiobiology

DTRA and provided their mission aims and described their interest in combined injury modeling. Dr. Terry Pellmar, retired Scientific Director of the Armed Forces Radiobiology Research Institute, chaired the panel and led the discussion. Dr. Gene McClellan provided an overview of the existing models available for radiation and combined injury. Dr. Darren Oldson followed with a description of the mechanistic approach to be used in the future. Dr. Daniela Stricklin initiated a discussion with the group on the modeling boundaries and provided basic overview of radiation, burn, and combined injury. The focus of the rest of the day was aimed at gaining input from the SMEs on:

- Primary organ systems that may be impacted by either radiation or burn injury
- Key underlying mechanisms that pose potential interactions within or between these organ systems in the case of combined radiation and burn injury
- Simplifying assumptions for use in a first iteration model
- Modeling approaches to the development of mathematical representations of these mechanisms
- Existing models, tools, and software that could be implemented
- Information gaps and follow-on research that could provide key insights into the model parameters

2. WORKSHOP DISCUSSIONS

2.1 MODELING BOUNDARIES

Changes in outcome (survivable to fatal) due to combined insults would be most likely in the moderate injury severity range. Therefore, modeling of moderate to severe sub-lethal injuries was considered most informative for the initial effort. In development of the model, priority will be placed on acute effects; intermediate and late term effects (greater than 60 days) will be addressed subsequently. Since both radiation and burn injuries have complex mechanisms with different time-dependent pathophysiological ramifications depending on dose and extent of injury, boundaries are needed to focus this initial effort. The parameters for these boundaries include dose for radiation, percent total body surface area (% TBSA) and depth for burn, and time scale of concern.

Table 2. Insult Boundary Parameters

Boundaries	Extent of Injury	Time
Radiation	Up to 6-8 Gy	0-60 days
Burn	30-35 %TBSA, partial thickness burn	0-60 days

While radiation (beta) burns represent an important hazard, the injury type is quite complex. For the purpose of the workshop and initial modeling, primary focus was placed on thermal injury, primarily flash burn. However, overlap and divergence between thermal injury and radiation-induced cutaneous injury was noted.

For the initial modeling effort, all injuries are considered without treatment. After functional models for the injuries alone have been developed, modeling of outcomes of standard care for the injuries will then be incorporated.

2.2 RADIATION INJURY

The lethal whole body dose for 50% of the population at 60 days ($LD_{50/60}$) for untreated radiation exposure is estimated to be 3.5-4.0 Gy (Goans 2009). Significant physiological impairment is observed between 1 and 5 Gy. Above 6-8 Gy, survival of radiation injury is considered to be unlikely without aggressive medical treatment. The threshold for lethality from radiation exposures combined with burn depends on several factors including the extent of the burn; however, SMEs agree that survival would be probable with exposures below 1 Gy in untreated combined injury (assuming the burn injury was otherwise survivable).

2.2.1 Organ system effects

Whole body radiation exposures of 1 Gy and greater cause a predictable series of clinical signs and symptoms that depend on the acute dose received. This injury is call acute radiation syndrome (ARS). ARS has been classically divided into sub-syndromes (hematopoietic, gastrointestinal, and cerebrovascular) depending on the prominence of the organ system manifesting symptoms.

The hematopoietic system is very sensitive to radiation because of the high mitotic activity of the progenitor cells of the bone marrow. Cytopenia can occur at doses as low as 1Gy. Lymphopenia is one of the first signs of radiation exposure, occurring within the first 24 hours post-radiation and reaching minimum cell counts within 48 hours. Blood counts for granulocytes and thrombocytes drop more slowly, reaching a nadir in 2 to 3 weeks. At moderate doses there is an initial spike in the neutrophil count the first few hours post exposure; then it too drops. The loss of lymphocytes and granulocytes results in an immune-compromised state that increases susceptibility to infection and potentially sepsis. With thrombocytopenia hemorrhage can result. Survival is possible if the radiation exposure does not completely destroy all bone marrow stem cells. With some progenitor cells remaining, blood cell populations can be restored.

With radiation doses of 5-6 Gy to 30 Gy, gastrointestinal (GI) effects also become evident. Loss of crypt cells in the intestine causes impaired motility and absorption; breakdown of the mucosal barrier leads to entry of enteric bacteria into the circulation and increased risk of sepsis. At doses of 12 Gy or greater, mortality from GI effects occurs within one to two weeks, which is prior to hematological death.

Doses in the range of 20-30 Gy and higher can cause lethality within two days due to the cerebrovascular syndrome. Seizures, hypotension, impaired cognition, and cardiovascular shock can be evident. Neurovascular effects can also evidence themselves at much lower doses and are thought to contribute to the prodromal effects that include nausea, vomiting, fatigue and weakness. Cognitive effects may be observed as low as 5 Gy, presumably from increased blood-brain barrier permeability resulting in edema (Fliedner 2001).

Cutaneous radiation syndrome (Peter 2005) may also be considered a part of ARS (Fliedner 2001), although acute local radiation events may occur separately as well as coexist with ARS (Goans 2009). The skin is therefore an important organ to consider in the modeling effort. Moderate doses of radiation can cause initial, transient erythema from an initial inflammatory response. Cutaneous effects can be dramatic at high doses which are of concern when there has been an acute localized exposure which can result from deposition in hot particles on the skin from fallout. The term “radiation/beta burns” has been used to describe the resulting lesions (blistering, desquamation, etc.); however, experts indicate that this term results in misclassification of the injury. The injury is more appropriately termed cutaneous injury. While acute cutaneous injury from radiation fallout will not be addressed in the first iteration of this modeling effort, radiation effects to the skin should be kept in mind since these effects would likely interact synergistically with cutaneous injury from thermal burn.

If an individual can survive the acute effects of ionizing radiation, damage to other organs becomes evident at later times and can, in severe cases, result in organ system failure. For example, radiation pneumonitis may develop after several weeks post exposure and can lead to lung fibrosis and death after several months even at doses as low as 6-7 Gy. One SME noted that pulmonary failure is a main cause of death in those who survive the hematopoietic sub-syndrome

of ARS. The kidney also exhibits some radiosensitivity and may be permanently damaged at doses as low as 4.5 Gy (Mettler 2008); however, the effects manifest from 6-12 months post exposure, which is later than the lung and GI effects. Liver effects may also play a prominent role when radiation exposure is combined with burn. For instance, in the Chernobyl accident, hepatic encephalopathy was a major cause of death in patients with extensive skin burns.

In patients who survive the hematopoietic and GI syndromes, the effects on these additional organs can lead to multi-organ dysfunction syndrome (MODS). In MODS, the damage to one organ can exacerbate damage to other organs and eventually result in multi-organ failure (MOF) (Fliedner 2005), which can be observed as late as 6 - 9 months post exposure or even later. In the Tokai-Mura criticality incident, all of the ARS patients had multi-organ involvement (Uozaki 2005) and one patient died after 210 days even after hematopoietic recovery due to multi-organ damage (Asano 2005). While MODS and MOF occur at the upper end of the dose range under consideration for the modeling work, it is important to note that the combined injury will likely shift the threshold for these effects as well as decrease the time to lethality for these endpoints.

2.2.2 Underlying mechanisms

ARS impacts all organ systems of the body and must be considered a systemic disease requiring integrated management. Radiation triggers multiple underlying and interconnected pathophysiological processes. As described above, a primary driver of injury from radiation exposure is gross cell loss. Apoptosis occurs in a number of organ systems with widespread effects. A number of laboratories are testing countermeasures for radiation injury that block apoptosis and have demonstrated increased survival in animal models (Whitnall and Pellmar 2007). Cell loss also leads to inflammatory and other systemic responses. Consequences of cell loss include the release of cytokines, which has secondary and tertiary effects including inflammation. Since cell loss occurs in several organ systems concurrently, the inflammatory response is experienced globally. It was also noted that CNS effects can impact the inflammatory response and result in dysfunctional overall signaling.

Early inflammation is considered an important and beneficial response of the body to injury. In fact, blocking the early inflammatory response in trauma can lead to mortality. The inflammatory cascade includes changes in both pro- and anti-inflammatory cytokines; severe damage can perturb the balance of the response. Uncontrolled inflammation can cause additional damage by increasing reactive oxygen species and hindering circulation necessary for tissues to repair and resume normal function. Extended inflammatory responses can cause long-term tissue damage such as fibrosis.

Other important pathophysiological responses to radiation injury are permeability changes that can be observed in the vascular and GI systems. A change in the permeability of the blood-brain barrier leading to edema can also occur. In the GI tract, some permeability change is due to cell loss from both cell death and impaired regeneration of new cells because of stem cell damage. Signaling also plays a role in permeability changes; loss of barrier function can be observed without loss of cells. For example, altered permeability of the gut is associated with mobilization of neutrophils. This important phenomenon occurs with burn injury and is likely to be an important consideration for combined injury.

Stress hormones such as cortisol, as well as oxidative stress, may contribute to some of the pathophysiological responses to radiation. These factors may also contribute to fatigability and weakness.

The pathophysiology of cutaneous injury from radiation at high doses parallels that of burn to some extent. In contrast to thermal burns, with radiation cutaneous injury the underlying stem cells can be damaged, causing a life-time of chronic reactions that cannot be resolved even by skin grafting.

2.3 BURN INJURY

2.3.1 Overview

Thermal burn injury may be characterized by the % TBSA affected, depth of skin penetrated, and uniformity of damage within the wound site. The LD_{50} for burn was approximated at 30-35% TBSA without aggressive intervention, depending on the location of the burn. It was noted that patients with burns on the face (eyes and ears) and extremities have poorer prognoses. Inhalation injury can often accompany thermal burn and arises from poisonous gases (e.g. CO), direct heat injury, and products of combustion (soot, ash; Mlcak 2007). Deep secondary (deep partial thickness) burns of substantial size would require skin grafting.

Table 3. Overview of Thermal Burn Injuries

Classification	Depth	Clinical Characteristics
Superficial thickness	Involves epidermis	Erythema and pain but no blisters evolve
Partial thickness – superficial	Involves papillary dermis	Blisters, clear fluid, and pain
Partial thickness – deep	Involves reticular dermis	Whiter appearance, fixed red staining, reduced sensation
Full thickness	Involves epidermis, dermis, and subcutaneous fat	Charred, thrombosed blood vessels, no pain
Subdermal	Involves underlying tissues, such as tendons, muscle, and bone	Charred, dry, brown or white without sensation

(References: Williams 2009, Clarke 1999)

A number of factors such as age, gender, and presence of inhalation injury can significantly influence the anticipated outcome for burn patients. Young children and the elderly in whom cardiovascular effects can be observed are less tolerant of shock; older children, however, have better outcomes. Male casualties generally tolerate burns of similar % TBSA better than

females; the opposite tends to be true of traumatic penetrating injury. The mechanisms for this discrepancy have not been fully elucidated (Choudhry 2005).

With partial thickness burns covering 20%TBSA or greater, burn shock becomes a significant, early contributor to pathology. Fluid loss from the wound and increased capillary permeability systemically increases within the first day. Capillary permeability tends to return to normal in about 36 hours and the threat of burn shock passes. The depth of burn (deep partial and full thickness) and the %TBSA impact the likelihood of developing burn shock. Without aggressive fluid resuscitation, burn shock is likely to lead to death. Large volumes of fluid, 20-25L of i.v. fluids over 24 hours, are necessary, but must be administered carefully to avoid compartment syndrome (swelling). Colloidal fluids are used to limit the edema and severe pressure in body tissues that might otherwise result. Even without treatment, most people can linger for days with severe burns. Inadequate control of fluid loss can result in renal failure.

After the risk of burn shock has passed, the burn patient usually experiences a stable latent period from day 3 to 7. After about a week, pneumonia and possible bloodstream infection can develop. At the same time, nutritional demand is great due to a hypermetabolic response (described below). Nutrition must be given orally since i.v. administration increases the risk of feeding bacteria in the blood stream and turning bacteremia into septicemia. However, GI absorption may be increasingly impaired as systemic inflammation impacts proper GI function.

The causes of mortality from thermal injury have changed over time. Historically, burn shock and wound sepsis were leading causes of death in burn patients; however, an adequate understanding of fluid resuscitation and antibiotic treatment of the wound has minimized the deaths occurring from these mechanisms. Today, the causes of death observed in thermal injury are more often due to sepsis arising from pathogens translocated from the lung or GI tract and systemic complications leading to multi-organ failure (Bloemsma 2008).

2.3.2 Organ system effects

As described previously, the severity of a burn depends on the size and depth of the cutaneous injury. Local and systemic effects result immediately and can last for an extended period of time. The general pathophysiology is similar for most burns that are more serious than superficial injuries (i.e., partial thickness burns and worse). Two primary causes of mortality in untreated thermal injury are shock and sepsis. Burn shock as described previously results from fluid loss both locally and systemically.

Sepsis resulting from burns differs from that from radiation. Viruses and fungi, in addition to bacteria, can enter the bloodstream and develop into a systemic infection. Pathogens can migrate from the wound site, lung, or gut. As with radiation injury, severe burn results in immune dysfunction, increasing vulnerability to infection, especially in the lung which can lead to pneumonia.

Since the skin wound itself is an important indicator in the prognosis of a burn patient, clinical examination of the wound is a critical diagnostic tool. If the burn wound begins to deteriorate, it may indicate systemic complications such as gastrointestinal dysfunction. Both bone marrow and gut are affected by burn injury, can influence other organ systems, and impact survival. The mechanisms leading to organ and immune dysfunction are elaborated below.

2.3.3 Underlying mechanisms

In addition to the direct, local effects from the wound in thermal injury, a series of systemic responses are also promptly initiated. Pro-inflammatory responses are exhibited in the first day or so. To balance the acute inflammatory response, anti-inflammatory mediators are released and down-regulation of pro-inflammatory mediators may be observed in some cases (Adib-Conquy 2009). In an attempt to balance the inflammatory response, release of both pro- and anti-inflammatory mediators continue for an extended period of time as the system responds to the local injury. However, secondary effects of the mediators can impact hematopoietic cells and lead to, for example, thrombocytopenia and neutropenia. In this way, immune suppression and even dysfunction can result. The inflammatory responses can also mediate gut barrier dysfunction, a phenomenon that also can be observed in acute radiation injury.

Many of the systemic effects observed in burn injury are impacted by multiple patho-physiological mechanisms. For example, impaired GI function in burn injury is associated with ischemia which results in increased nitric oxide levels (Gosain 2005, Magnotti 2005). Ischemia evolves from the hypovolemia and hypotension of fluid loss. The systemic inflammatory responses also impact ischemia in the gut. The inflammatory responses play a role in the system-wide apoptosis that occurs with burn injury. Other mechanisms affect organ-specific apoptotic activity (Gravante 2006). For example, corticosteroids play a role in the thymus and spleen while increased catabolism impacts muscle.

Another systemic effect in burn injury is a sustained hypermetabolic response that can persist for up to a year or longer (Jeschke 2008). Catecholamines and stress hormones are thought to drive the hypermetabolic response. Intense hypermetabolism increases nutritional demand and results in altered metabolism. Since catecholamine levels can mediate bone marrow suppression, the immunological state can be impacted. Therefore, in extreme cases, sustained hypermetabolism, catecholamine-mediated bone marrow suppression, and inflammatory-mediated immuno-compromise can lead to a complete immunological collapse.

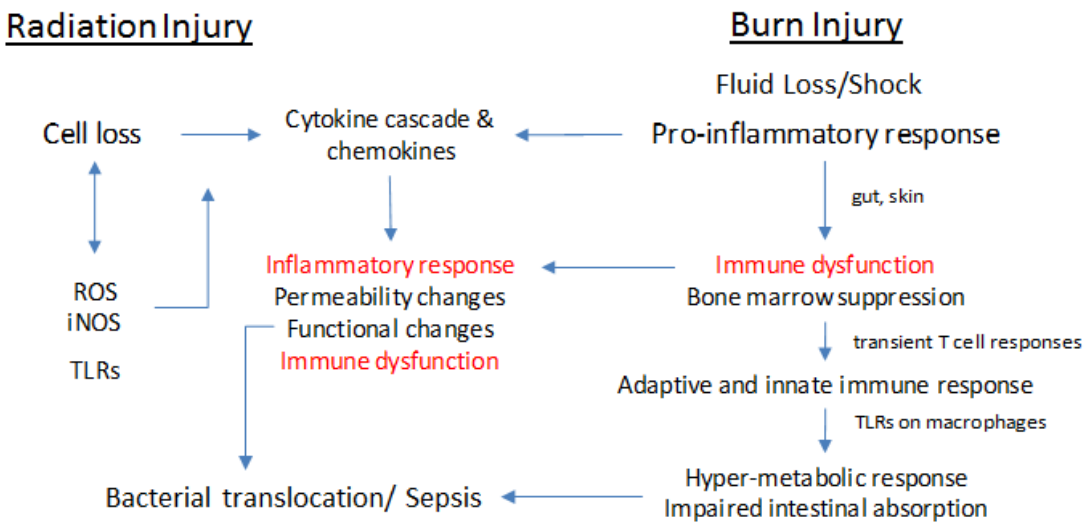
2.4 POTENTIAL INTERACTIONS IN COMBINED INJURY

Radiation combined injury is known to synergistically increase mortality, shorten the latent period before onset of symptoms of the manifest period, and impair wound healing (Messerschmitt 1965; Baum 1991). However, the pathophysiological processes causing these interactions are not well understood. The discussion of radiation and burn injury elucidated a number of overlapping mechanistic responses where synergisms could occur. The pathophysiological responses to both radiation and burn injuries overlap and might exacerbate responses of other systems or processes.

Since burn shock plays a prominent role in the outcome for burn patients (assuming no treatment), fluid loss must be considered an important process for modeling. Fluid loss can occur directly from the wound, excretion, perspiration, and edema in the burn case. Upper GI effects (vomiting) caused from radiation may also contribute to fluid loss. As mentioned previously, fluid loss will contribute to renal effects but can also lead to hypotension and hypo-perfusion, exacerbated by swelling and inflammation, which are also independently associated with each of these injuries. Inflammatory mediated responses to both injuries may interact to exacerbate delayed effects.

Because both burn and radiation elicit inflammatory responses, understanding the modulation of the inflammatory response by cytokines, both pro- and anti-inflammatory signals, was deemed critical to modeling of combined injury. Both positive and negative feedback loops exist, creating secondary cascades of cytokine production and potentially resulting in paradoxical responses. The process involves a number of cytokines and chemokines, including IL-6, IL-8, TNF-α, and TGF-β. Collectively, these responses impact the bone marrow and gut and their general functionality including immune response, cell proliferation, and barrier function of multiple organ systems. Figure 1 illustrates some of the effects leading to potentially synergistic inflammatory responses.

Figure 1. Schematic of Selected Mechanisms and Responses in Radiation and Burn Injury



*ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase; TLR, toll-like receptors.

A substantial risk of sepsis exists with acute radiation syndrome and with severe thermal injuries. Pathogens can enter the body when the skin or GI barriers are breached. In ARS, radiation-induced cell loss results in an immuno-compromised state and loss of integrity of the gut's barrier. In burn, the open wound offers a direct entry portal and a substrate for infection. In both injuries, immunological and inflammatory responses impact the overall ability of a host to respond to infection. The same pathophysiological mechanisms exacerbating the impaired permeability and integrity of the gut are called into play with both injuries, further enabling translocation of pathogens to the systemic circulation. Translocation of infection from the lung in pneumonia is particularly important in burn but may also be a consideration in ARS. Furthermore, significantly immune-compromised patients are susceptible to re-activation of dormant, endogenous pathogens, such as cytomegalovirus (CMV). Re-activation under such circumstances has proven to be a major complication leading to mortality in both injury types. Immune exhaustion and sepsis can lead to MOF.

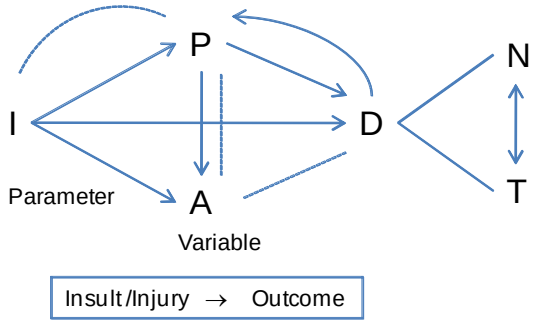
As treatments of acute injury have improved, mortality from shock and sepsis are less common and the observation of systemic complications leading to multi-organ failure are more common. In both ARS and severe burn, systemic responses linger for an extended period of time. Organ effects, such as pneumonitis, can be observed months after the initial injury. Combined injuries could shorten the time for these effects to manifest and could result in their occurrence at lower doses or milder insults. While the mechanisms underlying multi-organ failure are not fully understood, combined injury can be expected to increase the risk for MODS and MOF.

Early studies (see Messerschmitt 1965 and Baum 1991) demonstrate that radiation combined with burn results in synergistic increases in mortality. The existing data, however, are insufficient to understand outcomes at all doses and all burn severities. The proposed modeling effort may be able to shed light on the outcomes that can be anticipated and can help highlight and streamline research needed to understand and approximate predict responses to combined injury.

2.5 MODELING CONCEPTS

Aspects of modeling and approaches for constructing mathematical representations of complex systems were discussed, including strategies for parameterization and empirical verification. To stimulate discussion, a simplified conceptual framework for models representing injury and response was provided by an SME (Figure 2).

Figure 2. Simplistic Conceptual Model Framework



In the diagram, I represents any injury, insult, or infection; D represents any damage or dysfunction. For the discussion of radiation and/or burn, pro- and anti-inflammatory cytokines were chosen for variables P and A, respectively, as an example. The specific names of the mediators are considered of less importance than their general function. N and T were added to represent how damage or dysfunction also signals neural and other tissue responses. The arrows are representative of input parameters, rate equations, or other mathematical representations for processes. The diagram illustrates feedback loops to indicate how responses are interconnected.

In any injury many different types of damage or dysfunction can result, each with different magnitudes and time courses and each interconnected to a number of other ongoing systemic processes. Mechanistically, modeling a high level problem such as combined injury can be very complex and intricate. The construction of such a model requires several small models or

modules for the key components of the injury response. One or more modules may represent interactions on a molecular level while others might focus on a cellular or tissue level; a multi-scale approach is needed to integrate all of the modules.

A canonical model (using ordinary differential equations to describe relationships between modules) could be a starting point. Associations between empirical observations and outcomes could be used in part for simplification with greater detail included where necessary and where adequate data exist. The final product would be computational and modular, incorporating different granularities. To achieve this end will require an interdisciplinary approach and a collaborative effort to address the diverse aspects relevant to combined injury.

It was agreed that the overall model should be kept as simple as possible while still adequately predicting outcomes. Larger, more complex models tend to be more quantitative, gaining greater acceptance; however, they also incorporate considerable uncertainty and variability. Smaller models can actually be more useful.

2.5.1 Key Parameters for Modeling

Basic input parameters for radiation and burn include radiation dose and thermal energy deposited (cal/cm^2) to parameterize wound size and depth. For all responses to be modeled, time of onset and time course need to be considered. One of the earliest symptoms encountered in burn is shock, and therefore, fluid loss would be an important component to parameterize. The next response observed is immune dysfunction due to hematopoietic cell loss from radiation. Inflammatory responses are affected by both radiation and burn and interact with cell loss. Similarly, permeability changes, particularly in the GI system, are impacted by inflammation and cell loss. Because of the pathophysiological cascade, infection then becomes a concern. Based on these concepts, it is evident that the initial modeling work should include:

- Fluid loss
- Cell loss
- Inflammation
- Permeability changes
- Infection

2.6 RESEARCH GAPS AND VALIDATION

A comprehensive and quantitative assessment of combined radiation and thermal injury is not available. While several studies have explored the impact of a range of radiation doses, few if any have provided data on the impact of burn intensity, varying either TBSA or depth of damage. Animal studies are needed to resolve this information gap. However, Institutional Animal Care and Use Committee (IACUC) approval for these types of experiments is difficult to obtain.

Limited options exist for animal models of skin injury. While the pig is the best model available today, it has limitations. Pig skin is thicker than human skin, contains different immune-competent mast cells, and manifests erythema differently than human skin. The hairless guinea pig is another possibility but differs from human skin response more so than the swine model. It

may be possible to use information from existing databases of previous animal work. For some processes, such as burn shock and resuscitation, the human response is very different than in animal models and clinical data may be needed for extrapolation to combined injury.

There are large gaps in our understanding of signaling and mechanistic pathways, particularly in thermal injury. However, large research studies are underway to help evolve the mechanistic understanding of burn. The National Institute of General Medical Sciences (NIGMS) is funding a large-scale interdisciplinary research program entitled *Inflammation and the Host Response to Injury*. The "glue grants' from this program are supporting multi-center data collection and research to understand the mechanisms of MODS in burn. Burn centers include the University of Texas Medical Branch in Galveston, University of Washington in Seattle, the University of Texas Health Science Center in Dallas, and Loyola University in Chicago. In addition, the two registries might be useful resources for collecting data for thermal injury: National Burn Repository (American Burn Association) and the TRACS registry (American College of Surgeons Committee on Trauma).

Likewise, resources for radiation effects data include a U.S. and foreign Radiation Accident Registry (Radiation Emergency Assistance Center/Training Site, REAC/TS) and the SEARCH database system (World Health Organization-Collaborating Center for Radiation Accident Management). The U.S. Department of Health and Human Services has funding programs for basic research on mechanisms underlying radiation and combined injuries as well as applied research on diagnostics and treatment of these injuries. The research coming from these programs will be valuable resources for the modeling effort. Ongoing gene and protein expression research may provide insight on the breadth of modulators involved in responses to radiation exposures.

Since the proposed model involves a multi-system, interdisciplinary approach, close interaction with experimentalists and relevant experts should be maintained. These interactions will provide an avenue by which to fill data gaps as they are identified. It will also provide a way to validate components of the model as they are developed. For full model validation, historical data from accidents like Chernobyl may be used to test prediction of outcomes.

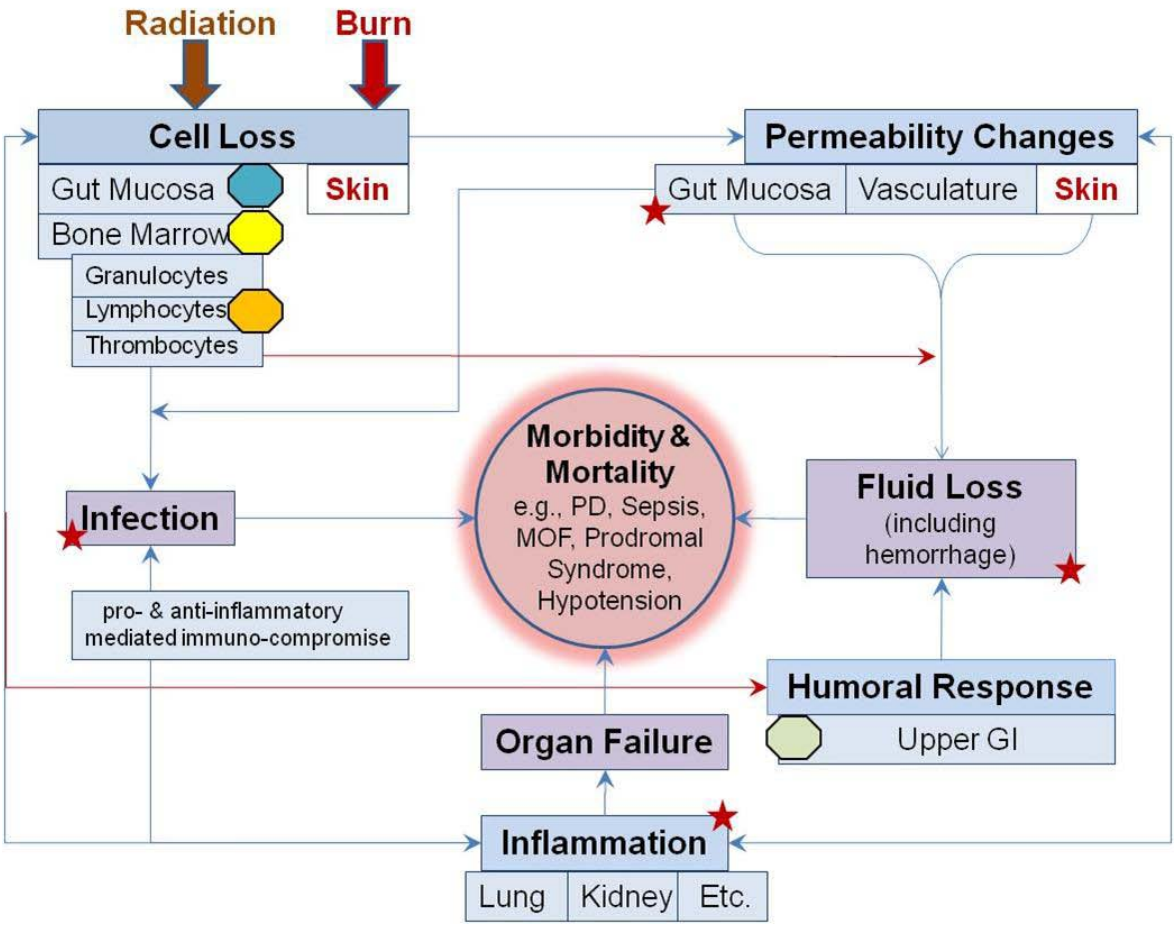
2.7 FUTURE COMPONENTS TO ADDRESS

A number of factors were identified that could impact outcomes in a model of combined injury. In an IND scenario in an urban setting, fires within damaged buildings could be a significant source of "flame" burns. In this case, inhalation injuries from smoke and chemicals involved in fires would be significant. The neutron component of this type of scenario may vary from that used traditionally. Accounting for the different quality of radiation involved in this scenario should be addressed. As mentioned previously, cutaneous injury from radioactive fallout should also be addressed in future efforts. Variable treatment of different injuries should be incorporated in to the model ultimately. While the modeling effort now focuses on estimating population response, it might be possible to parameterize the model to fit individuals.

3. CONCLUSIONS AND PATH FORWARD

By the end of the workshop, the group had agreed on some of the key components to be included in the combined injury model. In addition, there was concurrence that a modular approach would be the most effective way of combining complex physiological processes into an integrated model. Based on the input of the workshop participants, ARA staff refined the working model (Figure 3), which will build on the existing modules from the RIPD model. As discussed at the workshop, this will allow us to develop a model that will integrate radiation and burn injuries and to make refinements, as time and data permit, to improve the mechanistic base and the accuracy of the representation of the injuries. We will seek relationships with subject matter experts and research laboratories to provide broad expertise for incorporation of new data and perhaps the opportunity to experimentally test and validate model components.

Figure 3. Preliminary Block Diagram Illustrating the Inter-relationships of Components in a Physiologically-Based Model



* ★ indicates sites affected by burn injury; ⬭ indicates a module that exists in the current RIPD model.

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